



make medicines *child size*

Children's medicines: A situational analysis

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Executive summary

Improving child survival and caring for children affected by major diseases are global priorities included in Millennium Development Goals four and six.¹ The need for better access to appropriate essential medicines for children is well documented and recognized as an integral element to achieving development goals.

In 2006, the World Health Organization (WHO) began to lay the foundation for improving access to essential medicines for children by bringing together interested parties to share information and identify areas where more work was needed. While the pharmaceutical industry had done very little research and development of these medicines prior to this time, a small number of governments and civil society organizations had taken the first steps to bring about change.

A number of catalytic events and growing global interest advanced WHO's action to develop the Better Medicines for Children programme of work. Barriers limiting better medicines for children were identified, such as research and development gaps and factors limiting access and use, and recommendations were made to remove them. In 2007, the World Health Assembly passed resolution WHA60.20 calling for specific actions from WHO and Member States to improve access to better medicines for children. Later that year, WHO published the first WHO Model List of Essential Medicines for Children and launched *make medicines child size*, an international advocacy campaign to raise awareness and promote global action.

Since that time WHO has improved information sharing and stimulated action among interested international organizations, governments, industry, researchers, health-care providers, professional associations, academia, and civil society. Key guidance tools and documents to assist in the development and better use of medicines in children have been developed such as a web-based clinical trial registry, a Model Formulary based on the WHO Model List of Essential Medicines for Children, a Sources and Prices Guide, and a number of evidence based norms and standards. WHO has also secured

Recommendations made by WHO are having an impact

Based on research, WHO has identified fixed dose combinations and flexible solid oral dosage forms as being the best for delivering medicines to children. Through a complimentary process, Medicines for Malaria Venture developed and registered a cherry flavoured fixed dose combination dispersible tablet. The medicine was prequalified by WHO and added to the WHO Essential Medicines List for Children in 2009. As of June 2010, almost 42 million treatments of the medicine have been delivered to 32 countries.



funding from the Bill & Melinda Gates Foundation for the Better Medicines for Children project to promote research and development by providing evidence and guidelines, fill knowledge gaps, encourage access in selected countries, and advocate for better use of medicines in children at both the global and country level.

The global effort has resulted in significant progress to date and the identification of new challenges to be met. This document provides a brief overview of the situation of children's medicines in 2007 and where we are today.

1. Introduction

Over eight million children under five years of age die each year, many from illnesses such as diarrhoea, malaria, HIV/AIDS, tuberculosis and pneumonia.² Effective treatments exist for most of these conditions. However, these essential medicines are often not suitable for use in children. When paediatric dosage forms do exist, access to them can be problematic.

Lack of access to suitable medicines for children has led health-care providers and caregivers to estimate the dose by breaking tablets into quarters and halves, crushing tablets or opening capsules. Administering medicines in this way is difficult and can cause inaccurate dosing, which may result in reduced efficacy (due to under-dosing) and/or safety (due to over-dosing). Children are not small adults. They absorb and metabolize medicines differently. To be effective, medicines must be available in formulations that allow doses to be easily adjusted to reflect the size, state of development, and condition of a child. In addition, children, particularly newborns, may suffer from illnesses specific to their age group that require medicines not available for adults.

Several studies have examined factors that limit access to essential medicines for children, such as inadequate selection, safety, efficacy, quality, development and use of medicines in children. Three common reasons are lack of scientific evidence for efficacy and safety; lack of appropriate drug development and related market failure; and lack of knowledge and prescribing information for health-care providers. For example, many medicines have not been properly tested in children for safety and efficacy, making it difficult for national drug regulatory authorities to approve their use by children.

Better access to safe, effective medicines for children is recognized as an important part of improving child health and reducing child mortality. While there is a global need for better access to medicines for children, the impact is most acutely felt in developing countries. Improving child survival and caring for children affected by major diseases are global priorities included in Millennium Development Goals four and six.³ The World Health Organization (WHO) has actively promoted access to safe, effective, affordable and quality essential medicines for over thirty years. In 2006, WHO began to lay the foundation for

improving access to essential medicines for children by bringing together interested parties to share information and identify areas where more work was needed.

This document provides an overview of the situation of children's medicines in 2007, when the World Health Organization stepped up its work in this area and the current situation in 2010. It also highlights the challenges to making progress and the potential directions for future work and is based on previous studies and literature, as well as input from global partners. It is accompanied by a timeline in Annex 1.

2. Situation in 2007 – Where were we?

By 2007, the need for better access to appropriate essential medicines for children had been well documented. While the pharmaceutical industry had done very little research and development of these medicines, a small number of governments and civil society organizations had taken the first steps to bring about change.

In 1997, the United States introduced measures to promote the development and registration of medicines for children. The European Union passed similar legislative and regulatory changes that would come into effect in 2007. Several developed countries, including the United Kingdom and Australia, published prescribing information for the use of medicines in children. A number of international nongovernmental organizations, such as Medecins Sans Frontiers and the Ecumenical Advocacy Alliance, had begun their own programmes to improve access to medicines for children. Although these efforts improved the availability and use of medicines for children, in many cases their effects had not reached developing countries, or were focused on treatments for very specific illnesses.

2.1 Catalytic events

Over the course of 2006 and 2007, a number of significant events occurred, which advanced WHO's action. In 2006, WHO and the United Nations Children's Fund (UNICEF) held a consultation on essential medicines for children in Geneva. The meeting brought together interested partners to identify ways to address the lack of essential medicines for children and to review a draft workplan for WHO and UNICEF, which became the Better Medicines for Children programme of work. Topics discussed included availability, suitability, regulatory issues, safety and treatment guidelines.⁴

Also in 2006, WHO commissioned a review of some children's formulations on the 14th WHO Model List of Essential Medicines. The purpose of the review was to identify medicines with indications for use in children that were not on the current List. This review was considered at



the March 2007 Expert Committee on the Selection and Use of Essential Medicines. The Expert Committee made several changes to the List and recommended that a subcommittee be established to develop a complete list of essential medicines for children.

In 2007, the 60th World Health Assembly reviewed a report prepared by WHO on better medicines for children and passed resolution WHA60.20 calling for specific actions by WHO and Member States to address the global need for children's medicines.^{5,6} This recommendation was followed by Executive Board approval to establish a temporary subcommittee of the Expert Committee on the Selection and Use of Essential Medicines, leading to the publication of the first ever WHO Model List of Essential Medicines for Children in December 2007. The subcommittee also made recommendations about dosage forms, knowledge and research gaps, and suggested next steps to advance the agenda.⁷ Also in December of 2007, WHO together with stakeholders launched *make medicines child size*, to raise awareness and promote global action to ensure that children receive the right medicine in the right dose at the right time.⁸ International organizations, governments, industry, researchers, health-care providers, professional associations, academia, and civil society have endorsed the initiative.

In 2007, WHO conducted a survey to collect information on the availability and cost of twenty paediatric medicines in fourteen countries in central Africa.⁹ The survey reviewed national essential medicine lists and standard treatment guidelines to see if the selected medicines were included, assessed the medicines' availability in public and private health-care facilities, and estimated the cost to patients of five selected medicines. The results showed that there was a need for action in all of these areas to improve access to medicines for children.¹⁰

2.2 Barriers limiting medicines for children & recommendations to remove them

Through these catalytic events WHO and partners identified gaps in knowledge, research, development, regulations, legislation, and supply systems that needed to be addressed to improve access and use of medicines for children.

Research and development gaps

More research was needed to provide (1) the necessary specifications for medicines that did not exist, and (2) the safety and efficacy data for proper dosing in children for medicines that existed in adult formulations. Without this information manufacturers were not able to develop new medicines for children or adapt existing medicines so that they could be used safely and effectively in children. Examples of these types of medicines included those for second-line treatment of tuberculosis resistant to existing medicines, tuberculosis/HIV co-infection, and selected neglected diseases. Additional research was also needed to improve safety monitoring, namely identifying delayed adverse effects of medicines in children; to



determine characteristics of an optimum dosage form for children; and to develop independent evidence-based prescribing advice for health-care providers.

Gaps in the development of children's medicines were identified where the necessary child specific data existed but (1) medicines needed to be developed or (2) existing medicines needed to be adapted by the pharmaceutical industry to be safe for use in children. For example, fixed dose combinations are the recommended treatment for several illnesses since they reduce the number of tablets patients must take, which in turn improves adherence. However, challenges were identified relating to their development for use in children. The required ratios of active ingredients vary depending on the age, size and physiological condition of the child. And, fixed dose combinations are generally not needed in developed country markets, therefore studies on their use in children have rarely been done.

In 2007, reviews showed a lack of suitable dosage forms of priority medicines for children, such as fixed dose combinations for malaria and tuberculosis, and antibiotics for neonatal infections. While some fixed dose combinations were available for malaria and tuberculosis, none were ideal for use in children. Fixed dose combination formulations to treat HIV/AIDS in children were in development.

For some other children's medicines, the market had not proven sufficiently profitable to justify pharmaceutical investment. Therefore manufacturers were reluctant to undertake the research and development required to produce medicines for children. The market failure and related lack of development revealed a need to provide appropriate guidance and incentives for the pharmaceutical industry to develop children's medicines. Increased efforts were also needed to encourage procurement agencies, health-care providers, and parents to demand better medicines for children and, thereby, build the market. The pharmaceutical industry also identified the need for international quality and safety norms and standards for manufacturing formulations for children to guide development and production.

Complicating the development of children's medicines were the ethical concerns surrounding clinical trials involving children and the lack of global standards for testing efficacy and safety. For this reason many medicines have not been properly tested in children, making it difficult for national drug regulatory authorities to approve their use by children.

Poor access and use of children's medicines is further limited by a lack of regulatory guidelines and mechanisms to encourage the registration of medicines for use in children. Also, there is a lack of capacity in many countries to assess applications for registration.



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Access and use gaps

A number of factors limiting access and use of medicines for children were identified. In these cases children's medicines existed, but were not reaching those who needed them. Barriers to access and use included lack of information, lack of appropriate dosage forms, pricing, and supply system challenges. Essential medicines for children that were affected by these barriers included pain medication, particularly for palliative care; oral rehydration salts with zinc to treat diarrhoeal diseases; child specific antibiotics for pneumonia; and asthma medication.

Many medicines continue to be used in children "off-label". To better inform health-care providers of optimum use of medicines in children, the need for evidence-based prescribing information and comprehensive clinical treatment guidelines for health-care providers were deemed priorities.

Although WHO had recently developed the Model List of Essential Medicines for Children, very few countries had adapted their national essential medicines lists to include these medicines. Many countries base their procurement on their national essential medicines lists. If medicines were not on the list, it is unlikely that they would be available on the shelves of pharmacies and central medical stores.

Other barriers to the supply and use of medicines for children included inappropriate dosage forms, difficulty administering adult dosage forms in appropriate doses for children, high costs for shipping and storage, cold-chain challenges, and affordability.⁴

A complete listing of recommendations from WHA 60.20 and their current status is contained in Annex 2.

3. Situation in 2010 – Where are we now?

Since its inception, measurable progress has been made in WHO's Better Medicines for Children programme. Many of the identified actions required to improve access to safe, quality medicines for children have been accomplished and the results are becoming evident. This section provides an overview of this progress, some specific global and country level examples, and other gaps that have been identified.

Many achievements of the Better Medicines for Children programme have been made possible through the Better Medicines for Children project supported by the Bill & Melinda Gates Foundation since October 2008, as well as contributions from the Netherlands. This project has enabled WHO to promote research and development by providing evidence and guidelines, fill knowledge gaps, encourage access in selected countries, and advocate for better use of medicines in children at both the global and country level.



Development and regulation

To address the outstanding safety, development, and regulatory needs, strengthening the quality and quantity of clinical trial research in children, without subjecting them to unnecessary testing, is essential. The WHO International Clinical Trial Registry Platform has created the “Clinical Trials in Children” portal to make information regarding the quality and monitoring of clinical trials involving children available online.¹¹ A survey of current guidance for child health and clinical trials has been completed for WHO; the International Union of Basic and Clinical Pharmacology 16th WorldPharma in 2010 included a session to review challenges of conducting clinical trials in children; the International Federation of Pharmaceutical Manufacturers and Associations Pediatric Task Force completed a survey to gather information on the experience of conducting clinical trials in developing countries; and WHO standards for evaluating clinical trials in children in resource-limited settings are being prepared.¹²

The European Medicines Agency has also made significant contributions toward increasing safety and efficacy of medicine use in children while minimizing unnecessary risks. Its programme aims to: use data and safety monitoring boards as a standard requirement; use measures to minimize pain, distress, and fear; advocate for sparse sampling where possible; use modeling and simulation where possible; and allow for innovative design and analysis methodologies to limit the number of children exposed while maximizing information. The agency introduced its own clinical trial registry, which will be made publicly accessible.

Flexible solid oral dosage forms have been identified as the optimum form for children’s medicines. In December 2008, WHO hosted an informal expert meeting of pediatricians; pharmacists; clinical pharmacologists; and representatives of the European Medicines Agency, International Federation of Pharmaceutical Manufacturers and Associations, Medicines for Malaria Venture, National Institutes for Health, UNICEF, and the Bill & Melinda Gates Foundation. The group reviewed existing evidence on appropriate formulations of medicines for children and identified future research needed to improve the development of preferred dosage forms.¹³ The key outcome of the meeting was the recommendation that WHO promote flexible solid oral dosage forms as the optimum form for the majority of children’s medicines. A survey was subsequently developed to assess current administration practices and preferred formulations for children’s medicines in Tanzania. This survey model will be replicated in other countries. One outstanding question regarding this type of formulation is the stability of active ingredients when dissolved in breast milk.

Related to the identification of fixed dose and flexible solid oral dosage forms as being the most appropriate for children, the Medicines for Children Research Network has supported research into novel formulations for children such as flavored granules and sachets.¹⁴ The network, founded in the United Kingdom to facilitate industry and publicly funded studies, has also studied how existing adult medicines may be manipulated to be used safely and more easily in children, as well as building evidence for the use of extemporaneous



preparations. The Commonwealth Pharmacists Association has conducted a survey to gauge the extent to which extemporaneous preparations are used and what evidence to support existing formulations is available. This work has reinforced WHO's efforts by drawing on a broad network of researchers and experts. WHO has commissioned a review of existing guidance available on the use of extemporaneous preparations, which will go before the Expert Committee in March 2011.

Following pharmacokinetic analysis and a review of evidence, fixed dose combination recommendations and product descriptions were revised in 2009, for treatment of tuberculosis in children.¹⁵ Also, new WHO treatment guidelines for management of tuberculosis in children have recently been completed and published.

The 13th International Conference of Drug Regulatory Authorities in 2008, held a two-day pre-meeting entitled "Better Medicines for Children: the way forward". The meeting gathered, for the first time, regulators, industry, clinicians, civil society and academics to identify challenges and seek solutions to ensuring better access to medicines for children. More than 240 participants from 75 countries were in attendance.¹⁶ One of the meeting's recommendations was for WHO to establish a global network of drug regulatory authorities to work on how best to license medicines for children. The first meeting of the Paediatric medicines Regulatory Network was held in 2010, fostering global collaboration in the areas of regulatory standards and paediatric clinical trials. A website has been developed to provide a platform for communication and discussion of key issues and to facilitate the development and implementation of a consistent regulatory strategy.¹⁷

The WHO Prequalification of Medicines Programme began including paediatric formulations on the Expression of Interest list and has prequalified at least seven medicines for children.¹⁸

The International Federation of Pharmaceutical Manufacturers and Associations established a special Pediatric Task Force in 2008, to work with WHO and other interested parties; share industry's experience in pediatric drug development; and help improve the availability of treatments appropriately adapted to meet the needs of children, especially for conditions/diseases prevalent in developing countries. Since the task force was created its members have participated in various meetings hosted by WHO and other parties.

Consistent with WHO's identification of fixed dose combinations as the preferred formulation for children and flexible solid oral dosage forms as the optimum dosage form, the Medicines for Malaria Venture developed and registered a cherry flavoured fixed dose combination artemether-lumefantrine dispersible tablet in 2008. The drug was then prequalified by WHO and added to the WHO Essential Medicines List for Children in 2009. As of June 2010, almost 42 million treatments of the medicine have been delivered to 32 countries.



The challenge of how to promote the development and procurement of optimum dosage forms for children continues to be raised at various fora. Where flexible solid oral dosage forms exist, they are often not the dosage form selected by procurement and supply agencies. Without demand, manufacturers are less likely to produce them. To help ensure that children's medicines are produced and procured in optimum dosage forms, WHO has undertaken two reviews to learn more about how and why governments and procurement agencies select and procure particular medicines. Building on their recent experience Medicines for Malaria Venture, in cooperation with WHO, undertook a review of paediatric medicine policy decision-making in five countries to learn what barriers may exist to the uptake of the new medicine formulations. Results of the review were shared at the Second Partners meeting for Better Medicines for Children in 2010. A second review to better understand pharmaceutical manufacturer and procurement/supply decision-making processes, particularly with respect to flexible solid oral dosage forms has just begun. The results of this study will inform the development and implementation of a targeted communication strategy with a goal of bringing about changes in development and procurement behaviour.

UNICEF has been working on building the supply and demand networks for medicines for children. The work has focused on assisting with forecasting and consolidating demand, advocating for policy change at the national level, and providing supply chain modeling to support distribution of medicines from the source to the patient.

During 2010, WHO developed a tool to measure local pharmaceutical manufacturing capacity. An assessment using the new tool was completed in Ghana and initial results have been compiled.

In response to the need for norms and standards for quality and safety in the manufacturing of medicines for children, the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted new specifications for a number of medicines for children including for the treatment of HIV/AIDs, malaria and tuberculosis.¹⁹

Access and use

The first and second editions of the WHO Model List of Essential Medicines for Children were developed by the temporary subcommittee of the Expert Committee on the Selection and Use of Essential Medicines in 2007, and 2009, respectively, and later approved by the Expert Committee. The list will continue to be reviewed and updated every two years through the regular meetings of the Expert Committee.²⁰

Recognizing the challenge for some countries to incorporate the Model List of Essential Medicines for Children into their national essential medicines lists, WHO is developing a short list of medicines to treat priority diseases in children. This list will provide countries and procurement agencies with a list of the essential medicines that they should ensure are available to improve child survival.



The publication in 2010 of the WHO Model Formulary for Children has provided the healthcare, procurement, and pharmaceutical communities with dosage and treatment information for over 240 medicines contained on the WHO Model List of Essential Medicines for Children. For the first time, medical practitioners worldwide have access to standardized information on the recommended use, dosage, adverse effects, and contraindications of these medicines when used in children. A number of countries have developed their own formularies over the years, but until now there was no single comprehensive guide to using medicines in children.

The first and second editions of Sources and Prices of Selected Medicines for Children offer up-to-date information on the availability and price of 612 different paediatric formulations, selected from the WHO Model List of Essential Medicines for Children; therapeutic food; and vitamin and mineral supplements.

In an effort to improve the use of medicines in children and child health outcomes, WHO completed a review of different methods of changing doctors' prescribing practices.²¹ A meeting was held to evaluate the review and select effective interventions.²² As a result, WHO is currently updating the Pocket Book for Hospital Care of Children to provide healthcare workers with guidance in using essential medicines in relation to paediatric clinical treatment guidelines. To encourage the safe use of medicines in children and improved pharmacovigilance WHO developed *Promoting Safety of Medicines for Children*, a guide to monitoring medicine safety and use including adverse drug reactions, and pre- and post-market surveillance.²³

A medicine availability and pricing survey module has been developed for the Better Medicines for Children project.²⁴ It is an adaptation of the survey methodology developed by WHO and Health Action International. Using this tool and with WHO's support, Ghana collected information on the availability and price of selected medicines for children in 2010. The medicines surveyed were available in only 17-19% of private and public sector outlets. WHO plans to complete similar studies in Tanzania and two states in India. A separate investigation in India will examine the add-on costs in the supply chain that contribute to a medicine's final price. The medicine availability and pricing survey tool can also be used by other interested partners. The Ecumenical Pharmaceutical Network used the survey in Kenya, Chad and Uganda. The survey results and reports are currently being finalized.

At the country level, WHO has also been actively encouraging the use of the various new tools and publications. It has also been advocating for the inclusion of medicines for children in national essential medicines lists, treatment guidelines and procurement schemes. And WHO has been working with national drug regulatory authorities to expedite regulatory assessment of essential medicines for children. In India, this effort has resulted in the state of Chhattisgarh adopting an essential medicines list for children and using it as its principle procurement tool.



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WHO is not alone in these endeavors. The International Pediatric Association and the International Union of Basic and Clinical Pharmacology have been focusing on building capacity among pediatricians and clinical pharmacologists to demand better medicines for children, to improve the use of medicines in children, and to promote testing in the clinical environment. The European Union funded Global Research in Paediatrics project brings together over twenty collaborating organizations and more than a thousand researchers. The project will offer an international training programme in paediatric clinical pharmacology using distance learning tools, harmonize paediatric research tools, as well as share research strategies and plans to reduce duplication.

Complimenting WHO's efforts, the Clinton Health Access Initiative uses a six pillar approach to improving availability of medicines for children. The foundation has taken actions to influence access, affordable and sustainable prices, quality, increased supplier base, higher procurement, and broader transparency. In 2007, when the foundation began this approach together with UNITAID, there were few paediatric antiretrovirals on the market, and those that were available had much higher prices than the adult versions. In 2010, there are now over forty formulations, including fixed dose combinations that can be used in children. Thirty formulations have been specifically developed for use in children and ten adult formulations exist that are safe for use in children.

Even if medicines for children are available, they are of little assistance if they cannot be used properly. In many low-income settings there is a lack of functioning calibrated scales to weigh children and dose them appropriately. While under-dosing results in ineffective use of medicines, over-dosing can result in toxicity and unsafe use of medicines. Through the Children's Mercy Hospitals and Clinics' Taking the guesswork out of Pediatric weight Estimation initiative WHO is supporting the development of a dosing aid that can be used in any scenario to accurately estimate the weight of children and dose them properly.

Communications and advocacy

The *make medicines child size* initiative and its website have provided a platform for WHO to share updates on progress in the area of children's medicines, as well as communications materials. The homepage provides an overview of the issue, while links to other pages provide detailed background and access to meeting reports and publications resulting from the work. Since 2007, there have been four press releases relating to children's medicines. And, in 2010, WHO issued its first fact sheet on children's medicines. This short information piece is available on the WHO corporate communications page, as well as through the *make medicines child size* website.²⁵



4. Successes and challenges

Progress is being made in improving access to and use of medicines for children. This progress is dependent on the interest, commitment, and cooperation of a range of partners. A few common themes for success have been identified, including the use of a multi-stakeholder approach, engaging senior government officials, academia, clinical practitioners, policy makers and partners; the readiness for change among the engaged stakeholders; the use and strengthening of existing capacity; careful project coordination; and management support from WHO regional and country offices.

While a number of challenges have been encountered as this work has moved forward at the country level, many of them are not unique to children's medicines. The slow pace of policy change; navigating bureaucratic processes; allowing for adequate time for permissions and clearances; drawing on already stretched human resources; and the need to provide assistance in preparing background material and samples of proposals and letters are common occurrences in affecting policy change in any realm.

At both the global and country level, there is a need to consider how best to build the momentum that has been created and to ensure the sustainability of activities and funding beyond 2012. Continuous advocacy is needed to promote the uptake of available paediatric formulations, translating the evidence for their use into appropriate policy and then into practice. Of equal importance is the need to encourage industry's capacity and willingness to formulate medicines for children. To bring about long-lasting change, WHO welcomes all stakeholder groups to share information, mobilize their memberships, and work together toward addressing these challenges.

Example of success with an outstanding challenge

With the support of a broad network of experts, WHO has developed new treatment guidelines for children with tuberculosis and identified new recommended doses. Researchers have successfully combined the necessary active ingredients into a dispersible solid oral dosage form, as recommended by WHO – a significant accomplishment. However, to accommodate the required ingredients the “pill” is now the size of a Euro coin, too large for a small child to comfortably place in his or her mouth. The outstanding challenge is now for researchers, drug developers, and the pharmaceutical industry to work together to refine the prototype and turn it into a usable medicine.

5. Next steps

Since its inception, the Better Medicines for Children programme has continued to discover more areas that need to be addressed. Numerous spin-off activities have begun beyond the original scope of work envisioned, such as the need for and efforts to develop a dosing aid for use in low-income countries, or the full extent to which extemporaneous preparations are used and the need for a standardized approach.

Recently identified research and development gaps include (1) comparative effectiveness studies to help make the case to policy-makers and procurement agencies as to why they should shift from current purchasing practices to procuring the recommended dosage forms; (2) best options for delivery, labeling, and packaging of new medicines; (3) universal dosing aids for easy and safe administration of medicines for children; and (4) clinical evidence for priority medicines.

Newly realized gaps hampering the access and use of medicines for children are: (1) further assisting countries in guideline implementation; (2) growing systems for capacity building and training beyond the scope of those currently underway; (3) updating supply management tools; (4) expanding the scope of the work beyond currently engaged countries and partners; and (5) continuously promoting the uptake of new medicines.

To assist in making progress in some of these areas, better knowledge and networking among the international pool of human resources working in this field are needed, as well as common indicators for measuring progress.

Action will be taken in all of these areas as part of the Better Medicines for Children programme. Where possible synergies will be found with the Bill & Melinda Gates Foundation funded Better Medicines for Children project, which continues until 2012; work being undertaken by interested partners; and other WHO programmes.



Annex 1

Children's medicines – A timeline

1970s	Lack of studies about effects of medicines in children identified as a safety problem
1980-1990s	Pharmacologists and paediatricians lobby national governments and international bodies to improve development of medicines for children
1997	United States Food and Drug Administration introduces regulatory changes and incentives for the development of medicines for children
2000s	European Medicines Agency begins the process of identifying and drafting regulatory changes to encourage the development and registration of medicines for children and introduces Framework 7 programme (FP7)
2002	United Kingdom releases the first British National Formulary for Children
2004	Legislative proposal from European Union is put forward
2005	United Kingdom begins work on a paediatric medicine strategy
2005	World Health Organization identifies priority paediatric medicines for HIV/AIDS and revises the treatment guidelines
2005	Clinton Health Access Initiative begins paediatric medicine programme
2006	International Alliance for Better Medicines for Children holds a meeting bringing together professional associations and researchers resulting in the Shanghai Declaration
2006	European Union paediatric medicine regulations are adopted
2006	Medicines for Children Research Network is founded in the United Kingdom to facilitate industry and publicly funded studies
2006	WHO commissions a review of medicines on the 14 th Model list of essential medicines for use in children
2006	WHO and UNICEF hold consultation on essential medicines for children
2006	WHO carries out survey on availability and access to medicines for children in 14 African countries
2006	Finland promotes a World Health Assembly resolution on children's medicines
2007	New European paediatric regulations are implemented
2007	WHO submits report on children's medicines to the World Health Assembly Executive Board
2007	The World Health Assembly passes resolution WHA 60.20



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- 2007 WHO and UNICEF sign a memorandum of understanding to work together to improve access to better medicines for children
- 2007 WHO identifies research and development gaps for children's medicines
- 2007 WHO launches "make medicines child size" campaign
- 2007 WHO releases first Model List of Essential Medicines for children
- 2007 Clinton Health Access Initiative and UNITAID begin paediatric programme to reduce cost and increase access to paediatric antiretrovirals
- 2008 International Conference of Drug Regulatory Authorities hosts meeting on Better Medicines for Children
- 2008 International Federation of Pharmaceutical Manufacturers and Associations creates a Pediatric Task Force
- 2008 WHO informal expert meeting identifies flexible solid oral dosage forms as the optimum dosage form for children
- 2008 Ecumenical Advocacy Alliance launches letter-writing campaign to promote better access to medicines for children with HIV/AIDS
- 2008 Medicines for Malaria Venture develops and registers a cherry flavored fixed dose combination artemether-lumefantrine dispersible tablet
- 2009 WHO receives grant from Bill & Melinda Gates foundation to support research and country level work to improve access and use of children's medicines
- 2009 WHO and UNICEF release first guide for Sources and Prices of Selected Essential Medicines for Children
- 2009 WHO issues 2nd edition of the WHO Model List of essential medicines for children
- 2009 WHO hosts meeting to identify effective interventions to improve use of medicines in children
- 2009 WHO Expert Committee on the Selection and Use of Essential Medicines accepts flexible solid oral dosage forms as the optimum dosage form for children
- 2009 Fixed dose combination recommendations and product descriptions are revised for treatment of tuberculosis in children
- 2009 WHO country selection meeting in Ghana identifies partner countries for the Better Medicines for Children project
- 2009 European Union issues FP7 call for International Pediatric Initiatives
- 2010 WHO holds first meeting of the Pediatric medicines Regulators' Network
- 2010 WHO and UNICEF issue 2nd edition of Sources and Prices
- 2010 WHO releases the first ever WHO Model Formulary for Children
- 2010 WHO issues Fact Sheet on children's medicines



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- 2010 WHO finalizes treatment guidelines for children with tuberculosis
- 2010 WHO begins identifying manufacturer and supply chain barriers to the development, procurement, and supply of children's medicines in flexible solid oral dosage forms, with support from the Bill & Melinda Gates Foundation
- 2010 --- Country progress examples ----
 - Two states in India update their essential medicines lists to include medicines for children
 - Medical schools in India add pharmacology to curriculum
 - Ghana – completes survey on pricing and availability of select medicines for children
- 2010 International Union of Basic and Clinical Pharmacology 16th WorldPharma includes session to review challenges of conducting clinical trials in children
- 2010 UNICEF hosts meeting to consider extemporaneous preparations for use in children
- 2010 WHO develops a list of priority products for child survival and UNICEF hosts meeting on the topic
- 2010 UNICEF and WHO host meeting with manufacturers to promote development of appropriate formulations for children
- 2010 WHO supports the study of preferred formulations in Tanzania
- 2010 Dosing aid to estimate weight in resource limited countries developed with support of WHO
- 2010 WHO develops new treatment guidelines for tuberculosis in children



Annex 2

Children's medicines – WHA60.20 Recommendations and current status

The recommendations presented in this table are limited to those included in resolution WHA60.20. The Status column provides examples of actions taken as of October 2010. The list of actions may not include all activities.

Recommendation	Status
REQUESTS Member States to	(as of October 2010)
(1) identify suitable formulations for medicines for children and encourage their manufacture and licensing by regulatory authorities;	Fixed dose combinations and flexible solid oral dosage forms have been identified by the World Health Organization as the optimum form for children's medicines. (Page 6-7)
(2) investigate whether currently available medicines could be formulated to make them suitable for use in children;	The Medicines for Children Research Network has been studying how existing adult medicines can be used more safely and easily in children (Page 7)
(3) conduct surveillance of antimicrobial resistance of locally available and commonly prescribed medicines for children;	The WHO project funded by the Bill & Melinda Gates Foundation is providing assistance in Ghana to study antimicrobial resistance. http://www.who.int/childmedicines/progress/Accra_final.pdf
(4) encourage research and development of appropriate medicines for diseases that affect children, and to ensure that high-quality clinical trials for these medicines are conducted in an ethical manner;	The European Union and United States have created incentive programs for the pharmaceutical industry to encourage research and development; WHO liaises with industry to promote the development of medicines for children; and WHO as well as the European Union have created clinical trial registries for tests carried out on children.
(5) facilitate timely licensing of appropriate, high-quality and affordable medicines for children and innovative methods for monitoring the safety of such medicines, and to encourage the marketing of adequate paediatric formulations together with newly developed medicines;	The European Union and United States have made efforts to expedite the licensing of medicines for children and have introduced requirements for paediatric formulations to be developed with newly developed medicines. (Page 6) WHO is working in some countries to support efforts to implement pharmacovigilance programmes to monitor the safety of children's



Recommendation	Status
REQUESTS Member States to	(as of October 2010)
	<p>medicines. http://www.who.int/childmedicines/progress/Accra_final.pdf The WHO Paediatric medicines Regulators' Network aims to assist countries in sharing information and experiences to address this recommendation. (Page 7)</p>
(6) promote access to essential medicines for children through inclusion, as appropriate, of those medicines in national medicine lists, and procurement and reimbursement schemes, and to devise measures to monitor prices;	<p>The WHO Model List of Essential Medicines for Children is beginning to influence countries' national medicines lists. WHO is working with Ghana, Tanzania and two states in India to adopt the list supported by the Bill & Melinda Gates Foundation project. WHO has developed a medicine availability and pricing survey module that can be used by interested partners and Member States. (Page 9) WHO and UNICEF have released the Sources and Prices of Selected Medicines for Children. (Page 9)</p>
7) collaborate in order to facilitate innovative research and development on, formulation of, regulatory approval of, provision of adequate prompt information on, and rational use of, paediatric medicines and medicines authorized for adults but not approved for use in children;	<p>The Medicines for Children Research Network has been studying new formulations for children's medicines. (Page 7) Through the International Conference of Drug Regulatory Authorities and the Paediatric medicines Regulators's Network, WHO liaises with national regulatory bodies to streamline and expedite the licensing of medicines for (Page 7) The new WHO Model Formulary for Children provides independent information on the safe use of medicines included in the WHO Model List of Essential Medicines for Children. (Page 9)</p>
(8) use all necessary administrative and legislative means including, where appropriate, the provisions contained in international agreements, including the agreement on Trade-Related Aspects of Intellectual Property Rights, in order to promote access to essential medicines for children;	<p>The WHO Prequalification of Medicines Programme works with UNITAID to promote the development of quality essential medicines for children. The Clinton Health Access has taken actions to influence access, affordable and sustainable prices, quality, increased supplier base, higher procurement, and broader transparency. (Page 10)</p>



make medicines **child size**

Recommendation	Status
REQUESTS Member States to	(as of October 2010)
<p>REQUESTS the Director-General of WHO to:</p> <p>(1) (a) promote the development, harmonization and use of standards for clinical trials of medicines for children;</p> <p>(b) revise and regularly update the Model List of Essential Medicines in order to include missing essential medicines for children, using evidence-based clinical guidelines; and</p> <p>(3) promote application of such guidelines by Member States and international financing bodies, with initial focus on treatments for HIV/AIDS, tuberculosis, malaria and chronic diseases;</p>	<p>(a) WHO standards for evaluating clinical trials in children in resource-limited settings are being prepared (Page 6);</p> <p>(b) The first and second editions of the WHO Model List of Essential Medicines for Children were developed in 2007 and 2009 respectively. The list will continue to be reviewed and updated every two years through the regular meetings of the Expert Committee. (Page 8)</p> <p>(c) WHO promotes the inclusion of medicines for children in national essential medicines lists, treatment guidelines and procurement schemes at the country level, as well as with international procurement agencies. (Page 9)</p> <p>WHO has also developed new clinical guidelines for the treatment of HIV/AIDS, malaria, tuberculosis, and pain in children. (<i>Report on the Second Partners Meeting</i>)</p>
<p>(2) ensure that all relevant WHO programmes, including but not limited to that on essential medicines, contribute to making safe and effective medicines as widely available for children as for adults;</p>	<p>WHO's Essential Medicines and Pharmaceutical Policies department actively works with other WHO departments to promote improved access to better medicines for children.</p>
<p>(3) promote the development of international norms and standards for quality and safety of formulations for children, and of the regulatory capacity to apply them;</p>	<p>The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted new specification for medicines for children. (Page 8)</p> <p>The WHO Prequalification of Medicines Programme provides workshops around the world for national regulatory authorities and pharmaceutical manufacturers to promote Good Manufacturing Practices for medicines for children.</p> <p>The Paediatric medicines Regulators' Network shares experiences in applying norms and standards. (Page 7)</p>
<p>(4) make available evidence-based treatment guidelines and independent information on dosage and safety aspects of essential medicines for children, progressively to cover all medicines for children, and to work with Member States in order to implement such guidelines;</p>	<p>In 2010 WHO published the WHO Model Formulary for Children, which provides healthcare, procurement and pharmaceutical communities with dosage and treatment information for over 240 medicines contained on the WHO Model List of Essential Medicines for Children. (Page 9)</p>



make medicines **child size**

Recommendation	Status
REQUESTS Member States to	(as of October 2010)
	WHO has issued new and revised treatment guidelines for HIV/AIDS, malaria, tuberculosis and pain in children. (Page 7)
(5) collaborate with governments, other organizations of the United Nations system, including WTO and WIPO, donor agencies, nongovernmental organizations and the pharmaceutical industry in order to encourage fair trade in safe and effective medicines for children and adequate financing for securing better access to medicines for children;	WHO collaborates with UNICEF, the Clinton Foundation, UNITAID and the Global Fund as well as national governments to promote the procurement and supply of safe and effective medicines for children. In Ghana, a review of current expenditure on medicines for children will help to determine if current financing is adequate. http://www.who.int/childmedicines/progress/Accra_final.pdf
(6) report to the Sixty-second World Health Assembly, and subsequently as appropriate, through the Executive Board, on progress achieved, problems encountered and specific actions needed to further promote better access to medicines for children.	WHO reported to the 124 th Executive Board and the Sixty-second World Health Assembly on progress and challenges to date. http://apps.who.int/gb/ebwha/pdf_files/EB124/B124_33Add1-en.pdf



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- 2 World Health Statistics 2010. Geneva, World Health Organization, 2010.
- 3 Millennium Development Goals (<http://www.un.org/millenniumgoals/>)
- 4 Meeting report of the Joint WHO - UNICEF consultation on essential medicines for children, 9-10 August 2006, Geneva. (<http://apps.who.int/medicinedocs/documents/s14092e/s14092e.pdf>)
- 5 Better Medicines for Children Report by the Secretariat (http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_25-en.pdf)
- 6 Resolution WHA60.20 (<http://www.who.int/childmedicines/publications/WHA6020.pdf>)
- 7 Terms of reference for the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines (http://apps.who.int/gb/ebwha/pdf_files/EB121/B121_8-en.pdf)
- 8 Make medicines child size (hyperlink - <http://www.who.int/childmedicines/en/>)
- 9 The 14 participating countries in the WHO African Region comprised Cameroon, Chad, the Congo, the Democratic Republic of the Congo, Ethiopia, Ghana, Kenya, Mali, Nigeria, Rwanda, Senegal, Uganda, the United Republic of Tanzania and Zambia.
- 10 Robertson J, et al. What essential medicines for children are on the shelf? *Bull World Health Org*, 2009. (<http://www.who.int/bulletin/volumes/87/3/08-053645/en/index.html>)
- 11 <http://www.who.int/ictcp/child/en/>
- 12 <http://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf>
- 13 Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children (http://www.who.int/childmedicines/progress/Dosage_form_reportDEC2008.pdf)
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- 16 WHO Drug Information Vol 22, No. 4, 2008 (http://www.who.int/childmedicines/paediatric_regulators/Recommendations_ICDRA2008.pdf)
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